IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/518,344 Confirmation No. 9502
Applicant : Mersin et al.
Filed : November 30, 2004
Title : ORAL PHARMACEUTICAL PREPARATIONS COMPRISING ION EXCHANGE RESINS WITH ACTIVE SUBSTANCE LOADING AND PSEUDOPLASTIC GEL-FORMER THICKENERS
Group Art Unit : 1618
Examiner : Paul Dickinson

VIA EFS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Dr. Ins Heep, declares and states as follows:

1. I received a degree in pharmaceutical science ("3. Staatsexamen") in 1994 from the University of Marburg, Germany. Thereafter, I received a Doctor's degree in pharmaceutical technology in 1998 from the University of Bonn, Germany.

2. From 1999 to the present, I was employed by Bayer HealthCare AG and then subsequently Bayer Animal Health GmbH. My present position is manager of formulation technology, within the formulation technology department of Bayer Animal Health GmbH.

3. Under my direction and control, a study to compare the optical appearance and viscosity of compositions including pradofloxacin and other excipients was conducted. Four formulations were prepared as can

be seen on the attached supporting documents (Attachment 1). The pradofloxacin formulation of the present invention is listed as formulation number 1 and included pradofloxacin, amberlite IRP 64, sorbic acid, ascorbic acid, propylene glycol, xanthan, water, and vanilla flavor. Formulation number 2 included pradofloxacin, amberlite IRP 64, sorbic acid, ascorbic acid, propylene glycol, 0.7 g silica, vanilla flavor, and water. Formulation number 3 included pradofloxacin, amberlite IRP 64, sorbic acid, ascorbic acid, propylene glycol, 1.5 g silica, vanilla flavor, and water. Formulation number 4 included pradofloxacin, amberlite IRP 64, sorbic acid, ascorbic acid, propylene glycol, 3.0 g silica, vanilla flavor, and water.

4. There is no sedimentation at all in formulation 1 as can be seen from the attached picture. Formulations 2-4 all show sedimentation.

5. Formulation 1, with Xanthan, is thixotropic and has a yield point of about 13.6 Pa. Formulations 2-4, with Silica, are not thixotropic and they hardly have any yield point. A thixotropic system with a yield point is advantageous because phase separation or sedimentation is avoided below that yield point. This makes it easier to transport and store the formulations. Upon shaking the yield point is overruled and the system is as liquid as formulations without any yield point which makes them easy to administer. This dramatic difference in viscosity and yield point is not anticipated on the basis of the minor change in the composition.

6. The applicant further declares that all statements made herein are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dr. Iris Hoop

Date

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Pradofloxacin Oral Suspension, office action, LeA 36165

14.06.2010

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Amtsgericht Köln

The following formulations are compared to each other regarding the pharmaceutical quality. Thus, different formulations were manufactured according to the following table 1.

TABLE 1: INGREDIENTS OF THE COMPARED FORMULATIONS.

Ingredients [g / 100 ml]	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Pradofloxacin	2.5	2.5	2.5	2.5
Amberlite IRP 64	10	10	10	10
Sorbic acid	0.2	0.2	0.2	0.2
Ascorbic acid	0.02	0.02	0.02	0.02
Propylene glycol	30	30	30	30
Xanthan	**0.7**	-	-	-
Silica		**0.7**	**1.5**	**3.0**
Vanilla flavor	0.2	0.2	0.2	0.2
Water, demineralized	ad 100 ml	ad 100 ml	ad 100 ml	ad 100 ml

After manufacturing the formulations were stored at ambient room temperature (about 22 °C). Their viscosity and sedimentation behavior was determined. In table 2 parameters like type of viscosity or the yield point is given and in graph 1 sedimentation behavior can be seen.

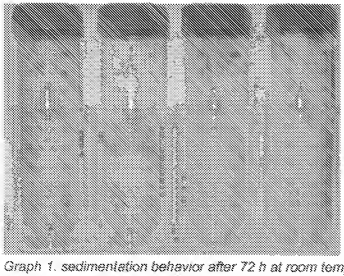
TABLE 2: VISCOSITY PARAMETERS OF THE FORMULATIONS.

Ingredients [g / 100 ml]	Form. 1	Form. 2	Form. 3	Form. 4
Xanthan	0.7	-	-	-
Silica		0.7	1.5	3.0
viscosity type	thixotropic	not thixotropic	not thixotropic	not thixotropic
yield point (tau)	13.6 Pa	0.6 Pa	0.5 Pa	1.5 Pa

The formulation with Xanthan is thixotropic and has a yield point of about 13.6 Pa. All formulations with Silica are not thixotropic and they hardly have any yield point.

A thixotropic system with a yield point is advantageous because phase separation or sedimentation is avoided below that yield point. This makes it easier to transport and store the formulations. Upon shaking the yield point is overruled and the system is as liquid as formulations without any yield point which makes them easy to administer.

Sedimentation behavior is easy to asses by the following picture (graph 1). It shows the stored formulations after 72 hours.



Graph 1. sedimentation behavior after 72 h at room temperature for the formulations with 0.7 % Xanthan, 0.7 % Silica, 1.5 % Silica, 3.0 % Silica

The formulation containing Xanthan (0.7 %) shows no sedimentation at all. All formulations containing Silica show significant sedimentation!

With 0.7 % Silica the strongest sedimentation occurs, with 1.5 % Silica the sedimentation is only slightly less and with 3.0 % Silica sedimentation is less but still half of the complete formulation -about 50 % sedimentation!

Formulation showing quick and sever sedimentation - like the ones with Silica- are difficult to dose accurately and they always bear the risk of not being homogenized sufficiently upon shaking. This is especially for elderly persons the case. Sometimes it is even impossible to redispers edimented suspensions due to a clocking of the dispersed particles ("caking").

A formulation with Xanthan has important advantages regarding the pharmaceutical quality due to the viscosity and the resulting sedimentation behavior.

Kind regards,

(Dr. Iris Heep)

BAH-RD-CFT-Lab. Head